Express Mail Label No.: EH[redacted]903285US
Date of Deposit: February 27, 2001

10/B
B. Webb
3/7/01
(AE)

Attorney Docket No. 21127-501 (formerly 14791-501)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS :	Perrin et al.		
SERIAL NUMBER :	09/314,698	EXAMINER :	Juliet C. Einsmann
FILING DATE :	May 19, 1999	ART UNIT :	1655
FOR :	Micro-Array Based Subtractive Hybridization		

Assistant Commissioner for Patents
Washington, D.C. 20231

Box AF

Response to Office Action Mailed August 28, 2000

In response to the Office Action ("Office Action") mailed August 28, please amend the application as follows.

In the Claims

Cancel claim 11.

OK to enter. JC 3/9/01

In claim 13, line 1, replace "11" with --26--.

In claim 14, line 1, replace "11" with --26--.

Add the following new claim:

B1

--26. A method for identifying multiple nucleic acids present in low abundance in a random sample of nucleic acid sequences, the method comprising:

(a) amplifying a random sample of nucleic acid fragments;

(b) immobilizing the random sample of nucleic acids on a solid surface in microarray format;

(c) hybridizing labeled probes from a DNA source to the immobilized nucleic acid fragments;

(d) identifying at least one immobilized fragment that hybridizes weakly or does not hybridize to the labeled probe;

(e) determining the sequence of the fragment identified in step (d); and

(f) reiterating steps (b) or (c) through (e), thereby identifying multiple nucleic acids present in low abundance in said random sample.--

REMARKS

Upon entry of the present amendment, claims 1-10 and 12-26 will be pending in the application. Claim 11 has been cancelled. New claim 26 has been added. Claims 13 and 14 have been amended to specify that they depend from claim 26 instead of cancelled claim 11. Support for new claim 26 appears in at least cancelled claim 11. No new matter has been added.

Claim 26 has been added solely to address various informalities noted by the Examiner with respect to now-cancelled claim 11.

The claims are rejected as obvious and indefinite, on various grounds.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 11 is objected to as containing various informalities. This claim has been cancelled and replaced by new claim 26. It is believed new claim 26 overcomes the rejections. Withdrawal of the rejection is requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-14 and 21 remain rejected as obvious over Kayne et al., (WO98/43088) ("Kayne") in view of Gress *et al.*, Mammalian Genome 3:609-612, 1992 ("Gress"). Claim 11 has been cancelled. The rejection is traversed as applied to claims 1-10, 12-14, 21 and new claim 26 for reasons advanced in Applicants' previous response, and also for the following reasons.

Claim 1, from which depends claims 2-10, requires hybridizing to an immobilized random sample of nucleic acid fragments one or more labeled probes corresponding to previously arrayed or sequenced fragments. Neither Kayne nor Gress describes or provides motivation for a method using a probe that corresponds to previously arrayed or sequenced fragments.

Kayne describes a method in which immobilized sequences are contacted with undefined nucleic acid sequences (see Abstract of Kayne and Applicants' previous Response). Gress describes a screening method in which cDNA arrays are screened with labeled cDNA pools derived from whole tissues (see Title and Abstract of Gress). According to the Examiner, the method described by Gress allows for screening of thousands of clones at a time and provides a method that is adaptable for automation.

Applicants respectfully submit that Gress lacks any motivation for substituting hybridization with an undefined nucleic acid sequence as taught by Kayne with a probe corresponding to previously arrayed or sequenced fragments, which is required by the claims. In fact, the probes used in the hybridization methods described by Gress include radiolabeled cDNA or total genomic probes (see, *e.g.*, the paragraph bridging pages 611-12 of Gress). There is no

suggestion in Gross, or in the combination of the references, of a method using one or more labeled probes corresponding to previously arrayed or sequenced fragments. Thus, to the extent Gress discusses labeled probes, it provides no suggestion for a method that includes the probe required by the claims. Accordingly, Gress cannot overcome the deficiencies of Kayne.

Independent claims 21, and 26 (corresponding to cancelled claim 11), and the claims depending therefrom, require identifying at least one immobilized fragment that hybridizes weakly or does not hybridize to a labeled probe. Neither Kayne nor Gress provides any suggestion or motivation for this step. Kayne describes a method in which sequences that do not hybridize to a collection of defined sequence are recovered as a pool of sequences. There is no suggestion in this reference, however, of identifying an immobilized nucleic acid that hybridizes weakly or does not hybridize to a probe molecule. Gress, as discussed above, does not overcome the deficiencies of Kayne because it, too, lacks any suggestion for identifying at least one immobilized fragment that hybridizes weakly or does not hybridize to a labeled probe. Thus, neither reference, when considered singly, or in combination, suggests the claimed invention.

Independent claim 12 requires, *inter alia*, repeatedly hybridizing labeled probes from a DNA source to an immobilized, microarrayed fragment, detecting hybridized fragments, and sequencing the hybridized fragments. Neither Kayne nor Gress provide motivation for the claimed step. As noted above, Kayne is concerned with subtraction libraries defined by the inability of a nucleic acid in solution to hybridize to an immobilized nucleic acid sequence. There is no suggestion in this reference of repeatedly screening a library of immobilized sequences, and detecting and sequencing immobilized fragments. Gress likewise lacks any motivation for repeatedly hybridizing labeled probes from a DNA source to an immobilized,

microarrayed fragment, detecting hybridized fragments, and sequencing the hybridized fragments. Thus, neither reference, when considered singly, or in combination, suggests the claimed invention.

In view of the foregoing comments, reconsideration and withdrawal of the rejections for obviousness over the combination of Kayne and Gress is requested.

Claims 15-17 and 22-24 are rejected as obvious over Pinkel et al., US Patent No. 5,690,894 ("Pinkel") and Schena at al., Science 270:467-70, 1995 ("Schena"). The rejection is traversed.

Claims 15 and 22, from which the remaining claims subject to the rejection depend, have been amended to specify that the nucleic acid fragments are immobilized on a coated glass surface. Pinkel cannot be combined with Schena to make obvious the claimed invention because the artisan would not turn to Schena to overcome the deficiencies of Pinkel.

Pinkel describes biosensor optical fiber arrays that transmit an optical signal from sensor end of the array, on which nucleic acids are immobilized, to a transmission end of the array. (See, *e.g.*, Abstract, FIGS. 1, 4, and col. 7, lines 1-23).

Schena, in contrast, reports that gene expression is monitored by monitoring emitted light with a laser fluorescent scanner containing a microscope object (see note 3 at page 470 of Schena). Thus, in Schena, fluorescence emitted by the coated glass surface is detected. This differs from the detection method described in Pinkel, which describes an apparatus and method in which light is detected as it is transmitted through optical fibers. Placing a coated glass surface, as described by Schena, on a optical fiber array described by Pinkel would block

transmission of light through the optical fibers. Therefore, placing the nucleic acids on a coated glass slide as taught by Schena, would frustrate Pinkel's teaching of nucleic acids added to optical fiber arrays that transmit an optical signal. Accordingly, one of ordinary skill in the art would not combine Pinkel and Schena to produce the claimed invention.

Reconsideration and withdrawal of the rejections for obviousness over Pinkel and Schena is requested.

Claims 18-20 were rejected as unpatentable over Pinkel in view of Schena and Maslyn. As described above, Pinkel and Schena are not combinable to produce the claimed invention. Thus, the combination of Pinkel, Schena and Maslyn do not result in the claimed invention. Reconsideration and withdrawal of the rejections for obviousness is requested.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

A petition for an extension of time and notice of appeal is enclosed. The Commissioner is hereby authorized to charge any additional fee due with this submission, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 21127-501.

Respectfully submitted,

Reg. No. 41,874

Ivor R. Elrifi, Reg. No. 39,529
Attorney for Applicants
c/o MINTZ, LEVIN
One Financial Center
Boston, Massachusetts 02111
Tel: (617) 542-6000
Fax: (617) 542-2241

Dated: February 27, 2001

David Johnson

TRADOCS:1443255.1(%XMF01!.DOC)